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EXAMINER

MILLER, MARINA I

ART UNIT PAPER NUMBER

1631

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/633,306

Applicant(s)

CASTLE ET AL.

Examiner

Marina Miller

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) 18 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☒ Claim(s) 2-17 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>8/6/04 (2); 11/4/04</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's election with traverse of Group I (claims 1-17 directed to a method for identifying marker genes whose level of expression predicts a biological response) in the reply filed on 1/19/2006 is acknowledged.

The traversal is on the ground(s) that the subject matter of claims 1-17 is sufficiently related, claims classified in the same classes/subclasses and a search and examination of the entire application would not place a serious burden on the examiner. This is not found persuasive because the inventions of Groups I-II are distinct. Each of the methods has different goals and steps and neither of the methods is required for the other method, as set forth in the Restriction/Election requirement mailed 9/19/2005. The examiner must search non-patent literature and foreign patents as well as U.S. patents and publications. In addition, the search required for each group is not coextensive with that required for any other group, therefore the examiner maintains that a search for both groups would be burdensome.

Applicants also election with traverse various species, as follows:

Species A: the magnitude of the difference in gene expression.

Species B: population stratified for its response.

Applicants did not state reasons for the traversal of the species election requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim.

Claim Objections

Claims 2-17 are objected to because of the following informalities: claims 2-17 recite “[a] method of claim” Claims 2-17 are dependent claims and should recite “the method of claim” Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-17 are directed to a method of identifying marker genes whose expression levels predicts a biological response in a cell or tissue comprising steps of obtaining gene expression data and analyzing the expression by a linear discriminate metric. However, not all processes are statutory under 35 U.S.C. 101. *Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility*. 1300 O.G. 4, on 22 November 2005 (published at the USPTO web site <http://www.uspto.gov/web/patents/patog/week47/OG/TOC.htm>). “To satisfy 101 requirements, the claim must be for a practical application ... which can be identified ... [*i.e.*] The claimed invention “transforms” an article or physical object to a different state or thing. [if not, then] The claimed invention otherwise produces a useful, concrete, and tangible result.” *Id.* section IV. C. 2 at 48-49 (the USPTO Web site’s version).

In the instant case, the claimed method steps “describe nothing more than the manipulation of basic mathematical constructs, the paradigmatic ‘abstract idea.’” *Id.* section IV. B at 47 (the USPTO Web site’s version). Specifically, the claimed method recites mathematical and/or statistical manipulations with gene expression data (*e.g.*, analyzing the expression by a linear discriminate metric recited in claim 1). The claimed method does not transform or reduce an article or a physical object (*e.g.*, expression data) to a different stage or thing because the “result” of the method (*i.e.*, analyzing gene expression data by a linear discriminate metric) is merely data (analyzed gene expression data) and is not equivalent to physical transformation. *Id.* section IV. C. 2 at 48-49. The claims do not recite tangible expression (*i.e.*, real-world result) of analyzed gene expression data, nor any recitation of an actual (*i.e.*, concrete) result in a form useful to one skilled in the art. Thus, the method does not recite steps of producing something that is concrete, useful, and tangible, and is not statutory.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation “analyzing the gene expression data to identify ... marker genes.” It is not clear whether the limitation “to identify” is intended to be an active, positive

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method step. Claims 2-17 depend from claim 1. As the intended limitation is not clear, claims 1-17 are indefinite.

Claim 1 recites the limitation “thereby identifying.” It is not clear whether the limitation “thereby identify” is intended to be an active, positive method step. Claims 2-17 depend from claim 1. As the intended limitation is not clear, claims 1-17 are indefinite.

Claim 1 recites in the preamble “a method of identifying ... marker genes whose level of expression predicts a biological response in a cell or tissue.” The method further recites steps of obtaining gene expression data and analyzing the expression. The claimed method does not recite a step of identifying markers whose expression levels predicts a biological response in a cell or tissue. The actual “result” of the method is “analyzing the gene expression.” Therefore, the relationship between the preamble and the method steps is not clear. As the intended limitation is not clear, claims 1-17 are indefinite.

Claim 10 recites a parameter z_i in the formula. However, neither the claims nor the specification defines the parameter. As the intended limitation is not clear, claims 10-12 are indefinite.

Claim 10 recites the limitations “the samples of group 1” and “the samples of group 2.” There is insufficient antecedent basis for this limitation in the claim because neither claim 1 nor claim 9 from which claim 10 depends recite samples of group 1 and samples of group 2. As the intended limitation is not clear, claims 10-12 are indefinite.

Claim 10 recites “the discriminate score for sample Z.” It is not clear whether “the discriminate score for sample Z” is intended to be “the discriminate score for each gene” recited in claim 9 or a different discriminate score. If the latter, there is insufficient antecedent basis for

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this limitation in the claim because claim 9 from which claim 10 depends does not recite a discriminate score for sample Z. As the intended limitation is not clear, claims 10-12 are indefinite.

Claim 10 recites “the variance” in lines 10 and 12. There is insufficient antecedent basis for this limitation in the claim because neither claim 1 nor claim 9 from which claim 10 depends recite a variance in the distribution of gene expression. As the intended limitation is not clear, claims 10-12 are indefinite.

Claim 11 recites the limitation “a discriminate score for each gene.” Claim 11 depends from claims 1, 9, and 10. Claim 9 recites “a discriminate score for each gene.” It is not clear whether “a discriminate score for each gene” recited in claim 11 is intended to be different from “a discriminate score” recited in claim 9. As the intended limitation is not clear, claims 11-12 are indefinite.

Claim 12 recited “the discriminate score for each gene.” Claim 12 depends from claims 1, 9, 10, and 11. Claims 9 and 11 recite the limitations “a discriminate score for each gene.” It is not clear which “discriminate score” is intended in claim 12, *i.e.*, a score recited in claim 9 or in claim 11. As the intended limitation is not clear, claim 12 is indefinite.

Claim 12 recited the parameters f_i ; X_i ; Y_j ; $i=1\dots t$; $j=1\dots n$ which are not expressly defined either in the claims or in the specification. As the intended limitation is not clear, claim 12 is indefinite.

Claim Rejections - 35 USC § 102

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 9-14, and 16-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Mendrick, WO 02/10453.

Mendrick discloses a method for identifying toxicity markers (p. 3) comprising obtaining gene expression data for test and control cells (p. 4, line 30 through p. 5, line 1; section Toxicity Prediction and Modeling, p. 15-16) and analyzing the gene expression by a linear discriminate metric that does not depend from the relative magnitude of responses (p. 16 and p. 39-42). Thus Mendrick anticipates claims 1-3. Mendrick discloses computing probability distributions (p. 42), thus anticipating claim 4. Mendrick discloses hepatotoxicity (p. 38 and claims 14-15), thus anticipating claim 5. Mendrick discloses a score function and a discriminate score, and specifically the same function disclosed in instant claim 10 (p. 41-42), thus anticipating claims 9-10. Mendrick discloses calculating a discriminate score for each gene by summing the instances (p. 42), thus anticipating claims 11 and 12. Mendrick discloses multiple discriminating genes (p. 16), thus anticipating claim 13. Mendrick discloses measuring mRNA (p. 30, line 9), thus anticipating claim 14. Mendrick discloses markers are stratifying patient population (p. 36-38), thus anticipating claims 16-17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6-7, 9, and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, *Science*, 286:531-537 (15 Oct. 1999), in view of Lindon, *Progress in Nuclear Magnetic Res. Spectroscopy*, 39:1-40 (2001), and further in view of Xiong, *Mol. Genet. and Metabolism*, 73:239-247 (6/27/2001).

Golub discloses a method for identifying marker genes for classifying cancer (abstract). Golub discloses obtaining gene expression data for variety of samples (*i.e.*, test and control) (see p. 531, two last full paragraphs; p. 53, notes 13 and 23). Golub discloses analyzing the gene expression data to identify marker genes by a “neighborhood analysis” method (p. 532). Golub discloses identifying marker genes for acute lymphoblastic leukemia and acute myeloid leukemia (532). Golub discloses cross-validation of markers (p. 534 and 535, fig. 4). Golub discloses markers are stratifying patient population. Golub discloses using 10, 24, and 38 samples (p. 536, notes 13 and 23). Golub discloses marker genes discriminating between test and control groups (p.531).

Golub does not disclose using a linear discriminate metric that does not include the magnitude of the difference in gene expression. Golub also does not disclose cells exposed to a toxin.

Lindon discloses application of a well-known pattern recognition method such as linear discriminant analysis (LDA) (p. 16-17), wherein a linear discriminate metric does not depend from the relative magnitude of response (p. 17). Lindon also discloses differential gene expression as a result of disease or toxicity (*e.g.*, effect of a drug) (p. 3). Lindon discloses multiple discriminants (p. 17). Lindon discloses measuring mRNA (p. 3). Lindon discloses determining a score function and discriminate score (p. 17).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Golub to use the analysis of Lindon, specifically, LDA, such as taught by Lindon, where the motivation would have been to use a pattern recognition method that performs better than other statistical methods and provides a practical and accurate method for analysis using gene expression, as taught by Xiong, p. 247.

Claims 4 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, *Science*, 286:531-537 (15 Oct. 1999), in view of Lindon, *Progress in Nuclear Magnetic Res. Spectroscopy*, 39:1-40 (2001), and further in view of Xiong, *Mol. Genet. and Metabolism*, 73:239-247 (6/27/2001), as applied to claims 1-3, 6-7, 9, and 14-17, and further in view of James, Functional Linear Discriminant Analysis for Irregularly Samples Curves, *J. of the Royal Statistical Society Series, B* 63:533-550 (Feb. 13, 2001).

Golub, Lindon, and Xiong make obvious the method of claims 1-3, 6-7, 9, and 13-17, as set forth above.

Golub, Lindon, and Xiong do not disclose determining probability and equal weight for each gene.

James discloses a well-known method of a linear discriminant analysis (abstract). James discloses determining probability and equal weight for all classes (p. 544, section 4.2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Golub, Lindon, and Xiong to determine probability and use equal weight for each gene, such as taught by James, where the motivation would have been to use one of the well-known ways to describe LDA and classify equally important classes, as taught by James, p 533 and 544.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, *Science*, 286:531-537 (15 Oct. 1999), in view of Lindon, *Progress in Nuclear Magnetic Res. Spectroscopy*, 39:1-40 (2001), and further in view of Xiong, *Mol. Genet. and Metabolism*, 73:239-247 (6/27/2001), as applied to claims 1-3, 6-7, 9, and 14-17, and further in view of MacGregor, *Toxicological Science*, 59:17-36 (2001).

Golub, Lindon, and Xiong make obvious the method of claims 1-3, 6-7, 9, and 13-17 as set forth above.

Golub, Lindon, and Xiong do not disclose hepatotoxicity.

MacGregor discloses a gene expression array for determining hepatotoxicity (p. 25).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Golub, Lindon, and Xiong for determining hepatic toxicity, such as taught by MacGregor, where the motivation would have been to conduct a large scale drug safety evaluation, as taught by MacGregor, p. 25, left col.

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Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Golub, *Science*, 286:531-537 (15 Oct. 1999), in view of Lindon, *Progress in Nuclear Magnetic Res. Spectroscopy*, 39:1-40 (2001), and further in view of Xiong, *Mol. Genet. and Metabolism*, 73:239-247 (6/27/2001), as applied to claims 1-3, 6-7, 9, and 14-17, and further in view of Mendrick, WO 02/10453.

Golub, Lindon, and Xiong make obvious the method of claims 1-3, 6-7, 9, and 13-17, as set forth above.

Golub, Lindon, and Xiong do not disclose the limitations recited in instant claims 10-12.

Mendrick discloses the same scoring function and discriminant score as those recited in instant claims 10-12.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Golub, Lindon, and Xiong to use specific scoring functions and discriminant scores, such as taught by Mendrick, where the motivation would have been to use both individual measurements of each gene and the calculated measurements of all combinations of genes to classify samples, as taught by Mendrick, p. 42.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mendrick, WO 02/10453, as applied to claims 1-5, 9-14, and 16-17, in view of Shao, *J. Am. Statist. Assoc.*, 66(422):486-494 (1995).

Mendrick teaches the method of claims 1-5, 9-14, and 16-17, as set forth above.

Mendrick does not teach cross-validation of markers.

Shao discloses linear model selection by cross-validation (abstract).

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It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Mendrick to use cross-validation, such as taught by Shao, where the motivation would have been to select a model having the best predictive ability, as taught by Shao (abstract).

Conclusion

No claims area allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-5, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph. D. can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**MARJORIE A. MORAN
PRIMARY EXAMINER**

Marjorie A. Moran
3/16/04

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MM